REMARKS

Reconsideration is requested.

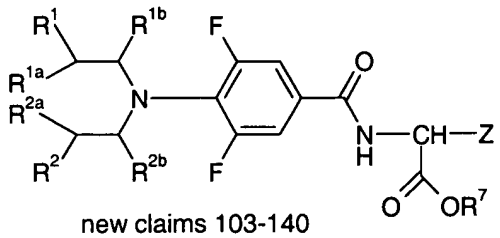
Claims 1-102 have been canceled, without prejudice. Claims 103-157 have been added to advance prosecution. Support for the amended claims may be found throughout the specification. Support for the recitations of the method claims for treatment of variety of cancers may be found, for example, on page 30, lines 2-13 of the specification. No new matter has been added.

The Section 112, first paragraph, rejections of claims 100-102 is moot in view of the above. The pending claims are submitted to be supported by an enabling disclosure.

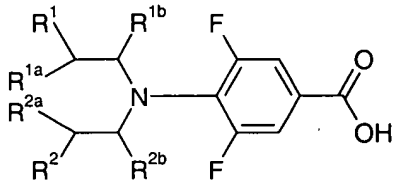
The Section 102 rejections of Claims 48-55, 66-83, 87-89, 91 and 100-102 over Springer (WO 94/25429), Claims 87-89 and 91 over Cozzi (WO 97/03957), Claims 87-89 and 91 over Karpavicius (Izvestiya Akademii Nauk SSSSR, 1979, (1), pages 51-58), Claims 87-89 and 91 over Karpavicius (Poiski Izuch. Protivoopukholevykh, 1977, 66-75), Claims 87-89 and 91 over Ivanova (Leikozoologiya, 1975, 4, 23-9), Claims 87-89 and 91 over Prasmickiene (Izvestiya Akademii Nauk SSSSR, 1969, (3), pages 643-6), Claims 87-89 and 91 over Jen (Huaxue Xuebao, 1965, 31(6), pages 486-92, 500), and Claims 87-89 and 91 over Davis (Journal of Chemical Society, 1950, pages 1331-7), are moot in view of the above.

The claims are submitted to be patentable over the art of record and consideration of the following in this regard is requested.

The pending claims are all directed to compounds wherein R^3 is -F, R^4 is -F, and R^5 is –H, which the applicants generally refer to as 3,5-difluoro compounds of the following general structure:



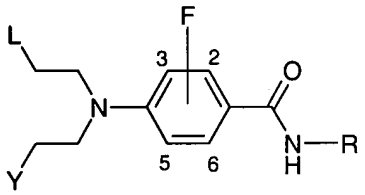
new claims 103-140



new claims 141-151

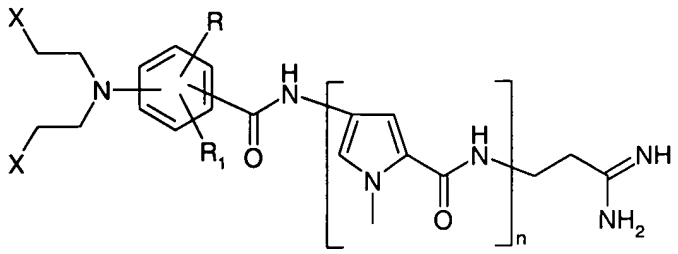
The claims are submitted to be patentable over the cited art and consideration of the following in this regard is requested.

Springer et al., WO 94/25429, teaches the following "monofluoro" nitrogen mustard prodrugs, more specifically, 2-fluoro and 3-fluoro nitrogen mustard prodrugs (see, e.g., page 3 therein):

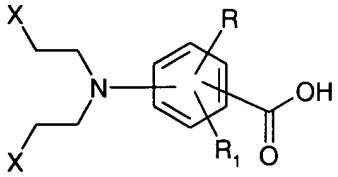


This document does not teach or suggest a 3,5-difluoro nitrogen mustard compound of the presently claimed invention.

Cozzi et al., WO 97/03957, describes the following "distamycin A" derivatives which are apparently useful as antitumour and antiviral agents:



These apparently active compounds are prepared from corresponding carboxylic acid chemical intermediates (see formula (III) on page 5 therein):



In all of these compounds, n is 2, 3, or 4; one of R and R_1 is -H, C_{1-4}alkyl, CF_3, or C_{1-4}alkoxy, and the other of R and R_1 is -H, C_{1-4}alkyl, CF_3, or C_{1-4}alkoxy.

This document does not teach or suggest a 3,5-difluoro nitrogen mustard compound of the presently claimed invention.

Each of the remaining six cited documents disclose benzoic acid compounds that are *unsubstituted* on the central phenylene ring.

These documents do not teach or suggest a 3,5-difluoro nitrogen mustard compound of the presently claimed invention.

The claims are submitted to be patentable over the cited art.

Attached, for completeness, is a copy of data submitted in the corresponding European application, for the Examiner's consideration.

The claims are submitted to be in condition for allowance and a Notice to that effect is requested.

Respectfully submitted,

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Annex A

Additional In Vivo Studies

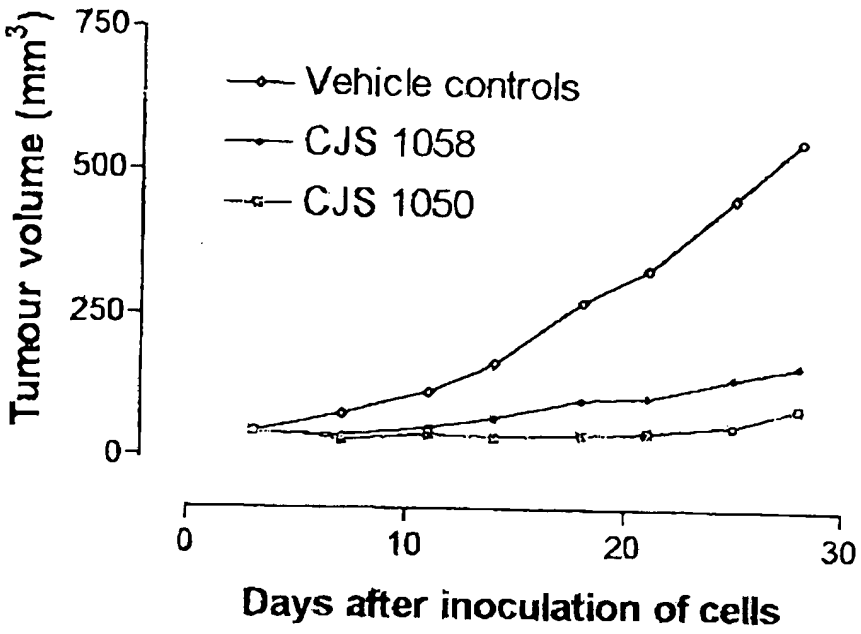
Additional *in vivo* studies were performed as follows. The animals used were mice of the strain CD1 with the nu/nu (nude) mutation and were obtained from the Charles River breeding company. This strain was used because the nude mutation leads to lack of development of the thymus, reducing the possibility of rejection of foreign tissue, and thus allowing human cancers to be modelled in these animals. On Day 0, each mouse received 10^7 MDA MB 361 human breast cancer cells by subcutaneous injection into the right flank. Either 100% or 50% of these cells were modified so as to stably express a surface tethered carboxypeptidase G2 (CPG2) mutant prodrug-activating enzyme (these modified cells are referred to as MDA MB 361-STCPG2(Q)3) (see, for example, WO96/03515). On Day 4, the mice received prodrugs by intraperitoneal injection (into the body cavity) in 3 doses spread over 24 hours. Subsequently, prodrugs were administered (again, by intraperitoneal injection (into the body cavity) in 3 doses spread over 24 hours) weekly (e.g., on Days 11, 18, etc.) for 7 weeks, except that no prodrugs were given on week 4 to allow the mice to recover any body weight lost through treatment. Each prodrug was studied using a group of 8 mice. Each prodrug was administered in a vehicle of 10% v/v DMSO in 1.26% w/v sodium bicarbonate. A control group of 8 mice received injections of vehicle only. Each prodrug was administered at "equitoxic" dosage, that is, a dosage which gives a maximum of 10% body weight loss in any mouse of a study group in a separate toxicity study. In each case, the claimed prodrug was less toxic than the corresponding unclaimed comparative drug, and so a higher dose could be administered. Body weight and tumour size were recorded (using calibrated callipers) twice or three times per week, during and after the treatment period. Tumour volumes were plotted against time to produce comparative growth curves for each prodrug. The experiments were carried out under licence, within the Animals (Scientific Procedures) Act, 1986.

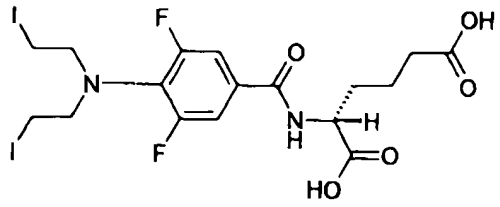
Results for the claimed di-iodo-di-fluoro and di-bromo-di-fluoro prodrugs and unclaimed (comparison) di-iodo-mono-fluoro and di-bromo-mono-fluoro prodrugs are shown on the following pages. In each case, the claimed di-fluoro compounds showed substantial and consistent improvement, as compared to the corresponding unclaimed (comparison) mono-fluoro compounds.

Annex A

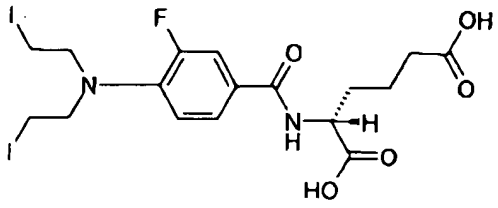
Group Mean Tumour Volumes
(100% MDA MB 361-STCPG2(Q)3 cells)

Dosage:
CJS-1050 = 600 mg/kg
CJS-1058 = 450 mg/kg





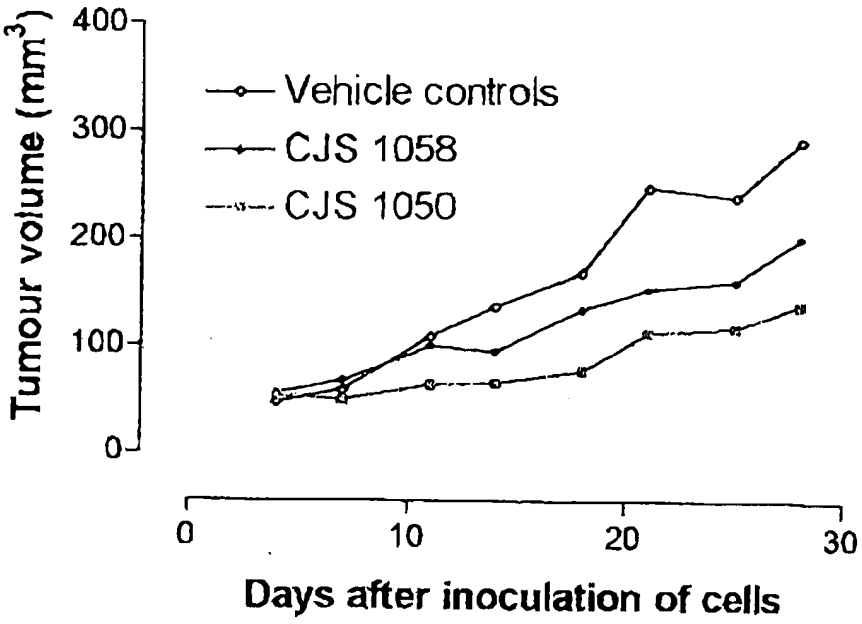
CJS 1050
"claimed compound"

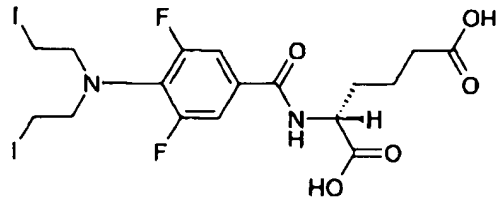


CJS 1058
"unclaimed comparative compound"

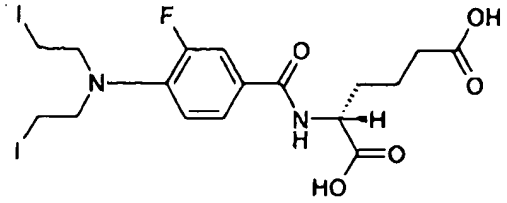
Group Mean Tumour Volumes
(50% MDA MB 361-STCPG2(Q)3 cells and 50% MDA MB 361 cells)

Dosage:
CJS-1050 = 600 mg/kg
CJS-1058 = 450 mg/kg





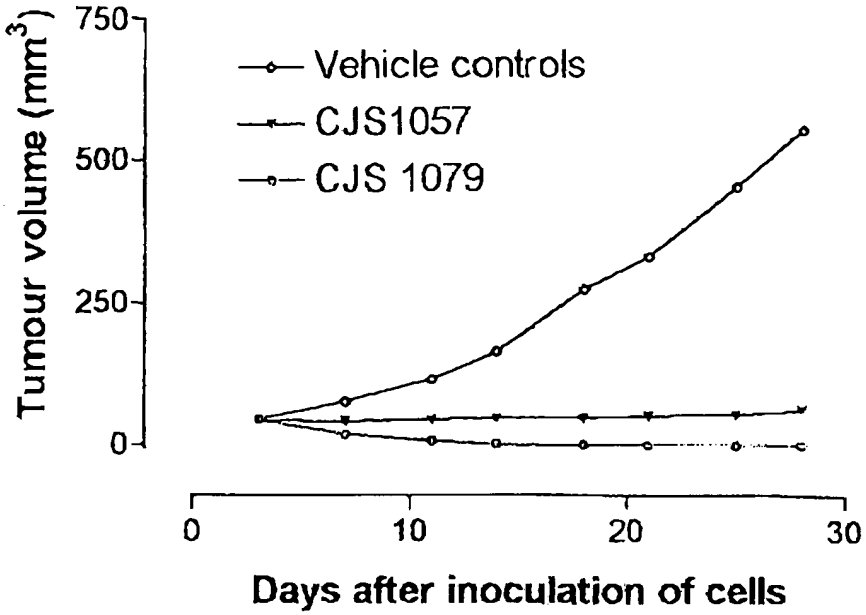
CJS 1050
"claimed compound"

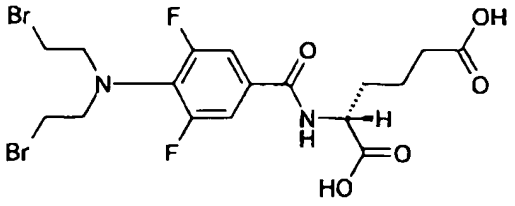


CJS 1058
"unclaimed comparative compound"

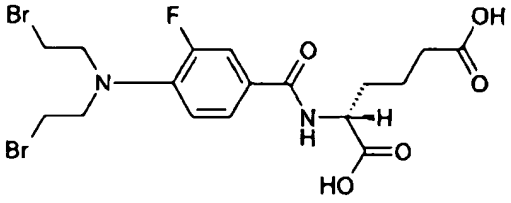
Group Mean Tumour Volumes
(100% MDA MB 361-STCPG2(Q)3 cells)

Dosage:
CJS-1079 = 1200 mg/kg (1st dose) and 600 mg/kg (remainder)
CJS-1057 = 360 mg/kg





CJS 1079
"claimed compound"



CJS 1057
"unclaimed comparative compound"